IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ASTRAZENECA AB, AKTIEBOLAGET HÄSSLE, ASTRAZENECA LP, KBI INC. and KBI-E INC.,	)	
Plaintiffs,	)	C.A. No. _____
v.	)	
TEVA PARENTERAL MEDICINES, INC., TEVA PHARMACEUTICALS USA, INC. and TEVA PHARMACEUTICAL INDUSTRIES LTD.,	)	
Defendants.	)	

COMPLAINT FOR PATENT INFRINGEMENT

JURISDICTION AND VENUE

1. This is an action for patent infringement and a declaratory judgment arising under the Patent and Food and Drug laws of the United States, Titles 35 and 21, United States Code. Jurisdiction and venue are based on 28 U.S.C. §§ 1331, 1338(a), 1391(b)-(c), 1400(b), 2201-02 and 35 U.S.C. §§ 271(a),(b), (c) and (e).

2. On information and belief, Teva Parenteral Medicines, Inc. ("TPM"), Teva Pharmaceuticals USA, Inc. ("Teva USA"), and Teva Pharmaceutical Industries Ltd. ("Teva Israel") (jointly and severally "Teva") have been and are engaging in activities directed toward infringement of United States Patent No. 5,877,192 (the "'192 patent"), by, *inter alia*, assembling and submitting pursuant to 21 U.S.C. § 355(b) New Drug Application ("NDA") No. 22-322 seeking FDA approval to manufacture commercially its proposed 20 mg/Vial and 40 mg/Vial products called "Esomeprazole For Injection" (hereinafter referred to as "NDA Products") containing the active ingredient esomeprazole.

3. In Teva's notice letter entitled "Patent Certification Notice – U.S. Patent No. 5,877,192" (hereinafter referred to as the "Notice of Certification"), Teva has indicated that it intends to market its NDA Products before the expiration of the '192 patent.

4. Teva's submission of NDA No. 22-322, in addition to service of its Notice of Certification, indicates a refusal to change its current course of action.

5. There has been and is now an actual controversy between Plaintiffs and Teva as to whether Teva infringes the '192 patent.

6. On information and belief, Teva is in the business of developing, manufacturing, marketing, and distributing generic pharmaceutical products, which are copies of products invented and developed by innovator pharmaceutical companies.

7. On information and belief, Teva USA, Inc. and/or Teva Israel, acting alone or in concert, have caused, actively encouraged and/or directed TPM to file NDA No. 22-322 with the United States Food and Drug Administration ("FDA"), and/or participated in the work related to the submission of NDA 22-322.

8. On information and belief, the Teva defendants are incorporated in Delaware, doing business in Delaware, have continuous and systematic contacts with Delaware, sell various products through the United States, including within Delaware, manufacture pharmaceuticals and pharmaceutical products that are sold and used throughout the United States, including within Delaware, and/or are engaged in activities together related to the subject matter of this action.

9. The Teva defendants are subject to personal jurisdiction in this judicial district.

THE PARTIES

10. Plaintiff AstraZeneca AB is a company organized and existing under the laws of Sweden, having its principal place of business at Södertälje, Sweden. AstraZeneca AB was formerly known as Astra Aktiebolaget.

11. Plaintiff Aktiebolaget Hässle is a company organized and existing under the laws of Sweden, having its principal place of business at Mölndal, Sweden.

12. Plaintiff AstraZeneca LP is a limited partnership organized under the laws of Delaware having its principal place of business at Wilmington, Delaware. AstraZeneca LP holds an approved NDA from FDA for intravenous esomeprazole sodium which it sells under the name NEXIUM I.V.®.

13. Plaintiff KBI Inc. ("KBI") is a Delaware corporation having its principal place of business at Whitehouse Station, New Jersey.

14. Plaintiff KBI-E Inc. ("KBI-E") is a Delaware corporation having its principal place of business at Wilmington, Delaware. KBI and KBI-E have exclusive rights in the United States to the '192 patent.

15. On information and belief, defendant Teva Parenteral Medicines, Inc. is a Delaware corporation having an office and conducting business at 2050 Springdale Rd., Cherry Hill, NJ 08003. On information and belief, defendant Teva Parenteral Medicines, Inc. is a wholly owned subsidiary of Teva Pharmaceuticals USA, Inc.

16. On information and belief, defendant, Teva Pharmaceuticals USA, Inc. is a Delaware corporation, having a principal place of business at 1090 Horsham Road, P.O. Box 1090, North Wales, Pennsylvania 19454. On information and belief, defendant Teva Pharmaceuticals USA, Inc. is a wholly-owned subsidiary of Orvet UK, which is a wholly-owned

subsidiary of Teva Pharmaceuticals Europe, which is a wholly-owned subsidiary of Teva Pharmaceutical Industries Ltd.

17. On information and belief, defendant Teva Pharmaceutical Industries Ltd. is an Israeli corporation, having a principal place of business at 5 Basel St., P.O. Box 3190, Petach Tikva 49131, Israel.

INFRINGEMENT OF U.S. PATENT NO. 5,877,192

18. Plaintiffs reallege paragraphs 1-17, above, as if set forth specifically here.

19. The '192 patent ("Exhibit A"), entitled "Method for the Treatment of Gastric Acid-Related Diseases and Production of Medication Using (-) Enantiomer of Omeprazole," was issued on March 2, 1999 to Astra Aktiebolag upon assignment from the inventors Per Lindberg and Lars Weidolf. The '192 patent was subsequently assigned to AstraZeneca AB. The '192 patent claims, *inter alia*, methods for treatment of gastric acid related diseases by administering a therapeutically effective amount of esomeprazole and pharmaceutically acceptable salts thereof and methods for producing a medicament for such treatment.

20. The '192 patent will expire on May 27, 2014 and pediatric exclusivity relating to the '192 patent expires on November 27, 2014.

21. Plaintiff AstraZeneca AB has been and still is the owner of the '192 patent.

22. Teva's Notice of Certification notified Plaintiffs that Teva had submitted an NDA to the FDA under 21 U.S.C. § 355(b), seeking the FDA's approval to manufacture, use, offer to sell and sell Teva's NDA Products as a generic version of the NEXIUM I.V.® product.

23. In the Notice of Certification, Teva notified Plaintiffs that as part of its NDA it had filed a certification of the type described in 21 U.S.C. § 355(b)(2)(A)(iv) with respect to the '192 patent. This statutory section requires, *inter alia*, certification by the ANDA applicant that the subject patent, here the '192 patent, "is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted . . . ." The statute (21 U.S.C. § 355(b)(3)(D)(ii)) also requires that the notice "include a detailed statement of the factual and legal basis of the opinion that of the applicant that the patent is invalid or will not be infringed." FDA Rules and Regulations (21 C.F.R. § 314.52(c)(6)) specify, *inter alia*, that such notification must include "[a] detailed statement of the factual and legal basis of the applicant's opinion that the patent is not valid, unenforceable, or will not be infringed." The detailed statement is to include "(i) [f]or each claim of a patent alleged not to be infringed, a full and detailed explanation of why the claim is not infringed" and "(ii) [f]or each claim of a patent alleged to be invalid or unenforceable, a full and detailed explanation of the grounds supporting the allegation."

24. On information and belief, at the time Teva's Notice of Certification was served, Teva was aware of the statutory provisions and regulations referred to in paragraph 23 above.

25. Teva's Notice of Certification, which is required by statute and regulation to provide a full and detailed explanation regarding non-infringement (see paragraph 23 above), does not allege and does not address non-infringement of the '192 patent claims. By not addressing non-infringement of '192 patent claims in its Notice of Certification, Teva admits that the commercial manufacture, use or sale of its NDA Products prior to the expiration of the '192 patent will infringe the '192 patent.

26. Teva's Notice of Certification, which is required by statute and regulation to provide a full and detailed explanation regarding unenforceability (see paragraph 23 above), does not address unenforceability or inequitable conduct of the '192 patent. By not addressing unenforceability or inequitable conduct of the '192 patent in its Notice of Certification, Teva admits that the '192 is enforceable and that there was no inequitable conduct concerning the '192 patent.

27. Teva's Notice of Certification did not provide the full and detailed statement regarding the '192 patent as required by, and therefore fails to comply with, the law, as specified in 21 U.S.C. § 355(b), and FDA rules and regulations, as specified in 21 C.F.R. § 314.52.

28. The commercial manufacture, use or sale of Teva's NDA Products will meet the limitations of one or more claims of the '192 patent and thus will infringe one or more of the '192 patent claims.

29. Teva has infringed the '192 patent under 35 U.S.C. § 271(e)(2) by filing an NDA seeking approval from the FDA to engage in the commercial manufacture, use or sale of a drug claimed in this patent, or the use of which is claimed in this patent, prior to the expiration of the '192 patent.

30. On information and belief, Teva's NDA Products, if approved, will be administered to human patients in a therapeutically effective amount to treat gastric acid related diseases by inhibiting gastric acid secretion.

31. On information and belief, administration of esomeprazole in Teva's NDA Products when compared to omeprazole decreases interindividual variation in plasma levels (AUC) during treatment of gastric acid related diseases.

32. On information and belief, administration of the esomeprazole in Teva's NDA Products when compared to omeprazole will increase average plasma levels (AUC) per dosage unit.

33. On information and belief, administration of the esomeprazole in Teva's NDA Products when compared to omeprazole will effect a pronounced increase in gastrin levels in slow metabolizers during treatment of gastric acid related diseases.

34. On information and belief, administration of the esomeprazole in Teva's NDA Products when compared to omeprazole will effect decreased CYP1A induction in slow metabolizers during treatment of gastric acid related diseases.

35. On information and belief, administration of the esomeprazole in Teva's NDA Products when compared to omeprazole will elicit an improved antisecretory effect during treatment of gastric acid related diseases, as further indicated by the proposed labeling submitted with Teva's NDA.

36. On information and belief, administration of the esomeprazole in Teva's NDA Products when compared to omeprazole will elicit an improved clinical effect comprising accelerated rate of healing and accelerated rate of symptom relief during treatment of gastric acid related diseases.

37. On information and belief, the amount of esomeprazole to be administered in Teva's 20 mg/Vial NDA Products will be about 20 mg total daily dose.

38. On information and belief the amount of esomeprazole to be administered in Teva's 40 mg/Vial NDA Products will be about 40 mg total daily dose.

39. On information and belief, Teva's NDA Products will be essentially devoid of (+)-omeprazole enantiomeric contaminant.

40. On information and belief, administration of Teva's NDA Products will occur at Teva's active behest and with its intent, knowledge and encouragement.

41. On information and belief, Teva will actively encourage, aid and abet administration of Teva's NDA Products with knowledge that it is in contravention of Plaintiffs' rights under the '192 patent.

42. On information and belief, Teva's NDA Products are especially made or especially adapted to inhibit gastric acid secretion and for use in the treatment of gastrointestinal inflammatory disease via the administration of a therapeutically effective amount of a pharmaceutical formulation containing esomeprazole. On information and belief, Teva is aware that its NDA Products are so made or so adapted. On information and belief, Teva is aware that its NDA Products, if approved, will be used in contravention of Plaintiffs' rights under the '192 patent.

43. In a letter dated April 7, 2008 and in order to further investigate whether Teva's NDA Products infringe the '192 patent claims, Plaintiffs requested access to certain documents, information and samples, as well as access to Teva's NDA No. 22-322 and the DMF.

44. Teva refused to provide Plaintiffs with access to any of the requested documents, information and samples.

45. Plaintiffs bring this suit, in part, to employ the judicial process and the aid of discovery to obtain information under appropriate judicial safeguards, to confirm that Teva's NDA Products infringe the '192 patent claims.

46. There has been and is now an actual justiciable controversy between Plaintiffs and Teva as to whether Teva has infringed, will infringe, or has contributed to, induced, aided and/or abetted infringement of or will contribute to, induce, aid and/or abet

infringement of the '192 patent by the acts stated above. This is so because Teva has engaged in and will continue to, without altering course, engage in and make meaningful preparation to engage, in the infringing acts stated above.

47. Plaintiffs have a filed a substantively identical action against the defendants in the United States District Court for the District of New Jersey. This action is being filed in the event that one or more of the defendants challenge personal jurisdiction over them or venue in the New Jersey Court. If the defendants do not challenge personal jurisdiction over them or venue in the New Jersey Court, plaintiffs plan to dismiss this action without prejudice.

WHEREFORE, Plaintiffs respectfully request the following relief:

(a) A judgment that the '192 patent has been and will be infringed by the Teva defendants;

(b) A judgment declaring that the effective date of any approval of Teva's NDA under Section 505(b) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355(b)) for the drug product "Esomeprazole For Injection" be no earlier than November 27, 2014, the expiration date of the last patent in suit, including pediatric exclusivity relating to the patent, that is infringed;

(c) A judgment declaring that Teva has not complied with the requirements of 35 U.S.C. § 271(e)(2), 21 U.S.C. § 355(b)(2), 21 C.F.R. § 314.50 and 21 U.S.C. § 314.52;

(d) A permanent injunction against any infringement of the '192 patent by Teva;

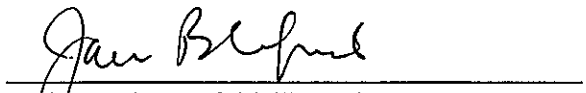
(e) A judgment that this is an exceptional case;

(f) An award of attorneys' fees in this action under 35 U.S.C. § 285;

(g) Costs and expenses in this action; and

(h) Such other relief as this Court may deem proper.

MORRIS, NICHOLS, ARSHT & TUNNELL LLP



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April 25, 2008

EXHIBIT A

US005877192A

United States Patent [19]

Lindberg et al.

[11] Patent Number: 5,877,192

[45] Date of Patent: *Mar. 2, 1999

[54] **METHOD FOR THE TREATMENT OF GASTRIC ACID-RELATED DISEASES AND PRODUCTION OF MEDICATION USING (-) ENANTIOMER OF OMEPRAZOLE**

[75] Inventors: **Per Lindberg**, Mölndal; **Lars Weidolf**, Västra Frölunda, both of Sweden

[73] Assignee: **Astra Aktiebolag**, Sodertalje, Sweden

[*] Notice: The term of this patent shall not extend beyond the expiration date of Pat. No. 5,714,504.

[21] Appl. No.: **833,962**

[22] Filed: **Apr. 11, 1997**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 376,512, Jan. 23, 1995, Pat. No. 5,714,504, which is a continuation-in-part of Ser. No. 256,174, Jun. 28, 1994, Pat. No. 5,693,818.

[30] **Foreign Application Priority Data**

May 28, 1993 [SE] Sweden 9301830
Apr. 11, 1996 [SE] Sweden 9601383

[51] **Int. Cl.**[6] **A61K 31/44**

[52] **U.S. Cl.** **514/338**; 514/819; 514/927

[58] **Field of Search** 514/338, 819, 514/927

[56] **References Cited**

U.S. PATENT DOCUMENTS

5,714,504 2/1998 Linberg et al. 514/338

Primary Examiner—Kimberly Jordan
Attorney, Agent, or Firm—White & Case LLP

[57] **ABSTRACT**

A method for treatment of gastric acid related diseases by inhibition of gastric acid secretion comprising administering to a mammal in need of treatment a therapeutically effective amount of the (-)-enantiomer of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole or a pharmaceutically acceptable salt thereof, so as to effect decreased interindividual variation in plasma levels upon administration. The use of the (-)-enantiomer of omeprazole to receive increased average plasma levels (AUC) upon administration of the same doses of the (-)-enantiomer of omeprazole compared to those of racemic omeprazole is also claimed, as well as an improved anti-secretory effect and a better clinical effect.

23 Claims, 3 Drawing Sheets

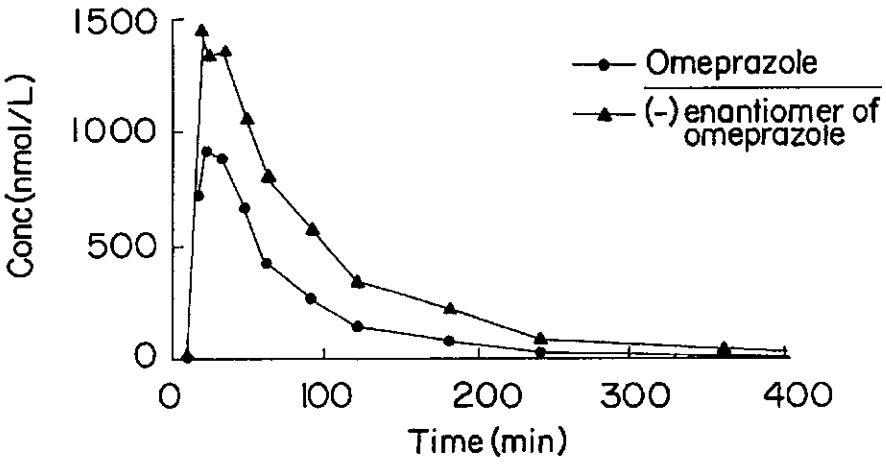
1500
1000
500
0
Conc(nmol/L)
0
100
200
300
400
Time (min)
Omeprazole
(-) enantiomer of omeprazole

FIG. 1

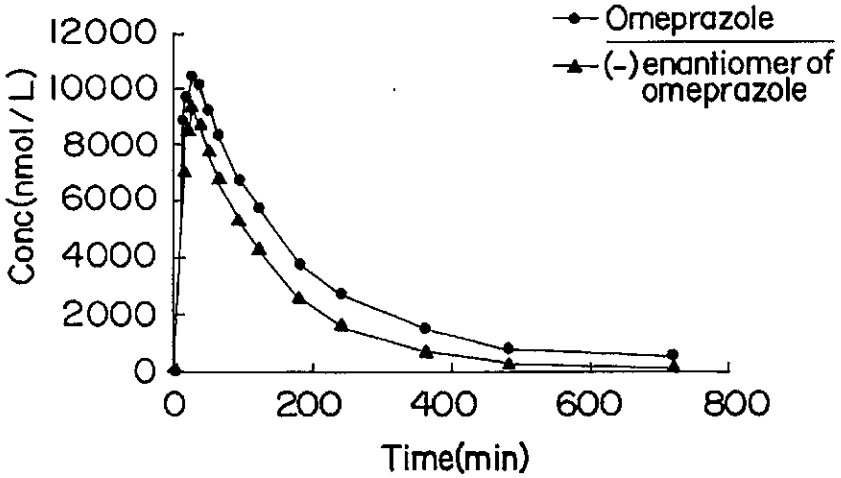
12000
10000
8000
6000
4000
2000
0
Conc(nmol/L)
0
200
400
600
800
Time(min)
Omeprazole
(-) enantiomer of omeprazole

FIG. 2

Mean plasma concentration (day 7)

AUC slow/AUC rapid		
(±)-omeprazole	(−)-omeprazole	(+)-omeprazole
10	3	30

AUC:area under the plasma concentration vs. time curve

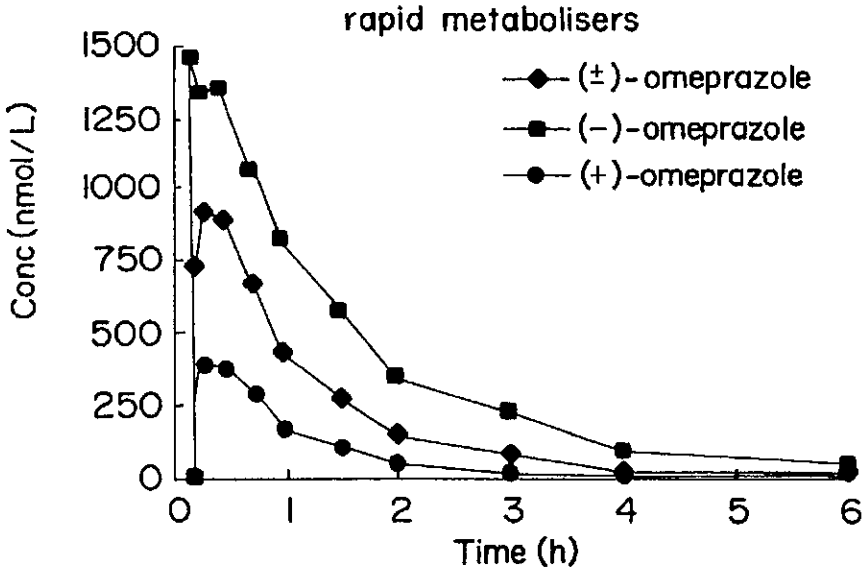

FIG.3A

Mean plasma concentration (day 7)

AUC slow/AUC rapid		
(±)-omeprazole	(−)-omeprazole	(+)-omeprazole
10	3	30

AUC:area under the plasma concentration vs. time curve

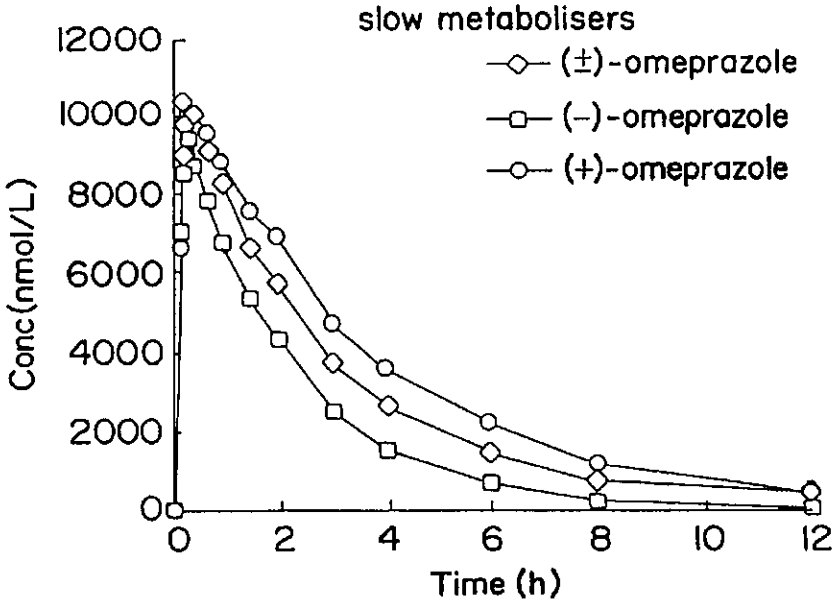

FIG.3B

METHOD FOR THE TREATMENT OF GASTRIC ACID-RELATED DISEASES AND PRODUCTION OF MEDICATION USING (-) ENANTIOMER OF OMEPRAZOLE

This application is a continuation-in-part of Ser. No. 08/376,512 filed on Jan. 23, 1995 now U.S. Pat. No. 5,714,504, which is a continuation-in-part of Ser. No. 08/256,174 filed Jun. 28, 1994, now U.S. Pat. No. 5,693,818.

The description of the salt forms of the single enantiomers of omeprazole and the process of making the same is herein incorporated by reference to copending Ser. No. 08/376,512.

FIELD OF THE INVENTION

The present invention is related to the use of one of the single enantiomers of omeprazole, i.e. the (−)-enantiomer of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole or a pharmaceutically acceptable salt thereof, in the treatment of gastric acid related diseases. The expression single enantiomer refers to the fact that the (−)-enantiomer is substantially free from its (+)-enantiomeric contaminant.

BACKGROUND OF THE INVENTION

The compound 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, having the generic name omeprazole, and therapeutically acceptable salts thereof, are described in EP 5129. The specific alkaline salts of omeprazole are described in EP 124 495. Omeprazole is effective as a gastric acid secretion inhibitor, and is useful as an antiulcer agent. In a more general sense, omeprazole may be used for prevention and treatment of gastric-acid related diseases in mammals and especially in man, including e.g. reflux esophagitis, gastritis, duodenitis, gastric ulcer and duodenal ulcer. Furthermore, omeprazole may be used for treatment of other gastrointestinal disorders where gastric acid inhibitory effect is desirable e.g. in patients on NSAID therapy, in patients with Non Ulcer Dyspepsia, in patients with symptomatic gastro-esophageal reflux disease (GERD), and in patients with gastrinomas. Omeprazole may also be used in patients in intensive care situations, in patients with acute upper gastrointestinal bleeding, pre-and postoperatively to prevent aspiration of gastric acid and to prevent and treat stress ulceration. Further, omeprazole may be useful in the treatment of psoriasis as well as in the treatment of Helicobacter infections and diseases related to these.

Omeprazole is a sulfoxide and a chiral compound, wherein the sulfur atom being the stereogenic center. Thus, omeprazole is a racemic mixture of its two single enantiomers, the (+)-enantiomer of omeprazole and the (−)-enantiomer of omeprazole. The absolute configurations of the enantiomers of omeprazole have been determined by an X-ray study of an N-alkylated derivative of the (+)-enantiomer in neutral form. The (+)-enantiomer of the neutral form and the (−)-enantiomer of the neutral form were found to have the R and S configuration, respectively. The conditions for the optical rotation measurement for each of the compounds mentioned above are described in WO 94/27988.

Different salts of the single enantiomers of omeprazole are also described in WO 94/27988. Specific processes for the preparation of the single enantiomers of substituted benzimidazoles are described in WO 96/02535. An oral pharmaceutical dosage form of omeprazole or one of its

single enantiomers is described in WO 96/01623. Other oral dosage forms for the (−)-enantiomer of omeprazole can be found in EP 247 983.

There are few studies on the single enantiomers of omeprazole. One previous in vitro study on inhibition of acid secretion in isolated gastric glands showed no significant difference in effect between the two single enantiomers of omeprazole and the racemic mixture, see Erlandsson P. et al, Journal of Chromatography 1990; 532: 305–319. It has also been shown that, when omeprazole was administered intravenously to one subject, the plasma levels of the two enantiomers were similar, see Cairns A. M. et al, Journal of Chromatography B, 1995; 666: 323–328.

More than 135 million prescriptions by doctors indicate that omeprazole is an effective and safe drug. Notwithstanding, omeprazole exhibits polymorphic metabolism, i.e. a few individuals (3% among the Caucasian populations and 15–20% among Orientals) metabolise omeprazole slowly (slow metabolisers) compared to the rest of the population (rapid metabolisers). Slow metabolisers of omeprazole will obtain higher than the average plasma concentrations of the drug. Since the inhibition of gastric acid secretion is correlated to the area under the plasma concentration versus time curve (AUC), a more pronounced effect from omeprazole is expected in these slow metabolising individuals. A less interindividual variation, i.e. especially slow versus rapid metabolisers, and on the average higher plasma levels, giving higher dose efficiency in patients, could be of therapeutic benefit. Thus, one of the enantiomers of omeprazole, referred to as the (−)-enantiomer of omeprazole, or a pharmaceutically acceptable salt thereof, is hereby claimed to be an improved alternative to omeprazole in the treatment of gastric acid related diseases resulting in higher dose efficiency and in less interindividual variation in plasma levels (AUC), both between rapid and slow metabolisers and within the group of rapid metabolisers.

SUMMARY OF THE INVENTION

The use of the (−)-enantiomer of omeprazole, or a pharmaceutically acceptable salt thereof, in the treatment of gastric acid related diseases as a mean to decrease interindividual variation in plasma levels compared to omeprazole is claimed. The use of the (−)-enantiomer of omeprazole to receive increased average plasma levels (AUC) of the substance compared to those of racemic omeprazole and thereby a higher dose efficiency is also claimed.

DETAILED DESCRIPTION OF THE DRAWINGS

FIG. **1** shows the mean plasma levels of racemic omeprazole and the (−)-enantiomer of omeprazole at steady state (Day 7) in rapid metabolisers following administration of 15 mg doses of each substance.

FIG. **2** shows the mean plasma levels of racemic omeprazole and the (−)-enantiomer of omeprazole at steady state (Day 7) in slow metabolisers following administration of 60 mg doses of each substance.

FIGS. **3***a* and **3***b* show the mean plasma levels of racemic omeprazole, the single (−)-enantiomer of omeprazole and the single (+)-enantiomer of omeprazole at steady state in rapid and slow metabolisers following administration of 15 mg and 60 mg doses of each substance, respectively. The figure sheet also comprises the ratios between the mean AUCs at steady state of slow and rapid metabolisers.

DETAILED DESCRIPTION OF THE INVENTION

Omeprazole is metabolised mainly in the liver by the cytochrome P450 system (CYP). Metabolism can be defined

as the property of the body to transform lipophilic compounds into hydrophilic derivatives, which more easily can be excreted from the body. The metabolism can generally be divided into phase I and phase II reactions. During a phase I reaction, polar groups are formed via oxidation, hydroxylation, or hydrolysis. These reactions are mainly associated with the CYP enzymes. Phase II reactions are conjugation reactions, in which even further hydrophilic moities are attached to the drug or to its metabolites.

CYP is a superfamily of enzymes. Each family consists of one or more subfamilies and each subfamily contains one or more specific CYP isoforms. Apart from metabolising drugs, the CYP isoforms also have the property to metabolise endogenous compounds, such as steroids, fatty acids, and prostaglandins.

With respect to drug metabolism in man, three families, CYP1, CYP2, and CYP3 or, more specifically, six different CYP isoforms within these families are of particular importance. Each isoform demonstrates a certain substrate specificity. The expression of these enzymes is under genetic control, which is one of the reasons for the interindividual variation in rate and extent of metabolism demonstrated for most drugs. Moreover, at least two of the CYP isoforms, CYP2C19 and CYP2D6, are polymorphically expressed. Thus, a few individuals among the population, i.e. the slow metabolisers, lack or express a mutated form of the relevant CYP isoform, and consequently metabolise substrates for this isoform slowly. Metabolism still occurs in these slow metabolisers, although at a lower rate, because it is switched to other CYP isoforms which are less important for the metabolism of the substrate in the rest of the population.

Omeprazole is known to be a substrate for the polymorphically expressed CYP2C19. In vitro studies in human liver microsomes have surprisingly indicated that the (−)-enantiomer of omeprazole is less metabolised by CYP2C19 than omeprazole. In agreement with this, it has also been found, according to the present invention, that administration of the (−)-enantiomer of omeprazole or an acceptable therapeutical salt thereof results in a less pronounced difference in plasma levels between slow and rapid metabolisers.

Some studies have been published indicating that slow metabolisers, with higher than average plasma concentrations of omeprazole, are more prone to develop hypergastrinemia (Chang M. et al. Br J Clin Pharmacol 995; 39: 511–518, Caraco Y. et al. Clin Pharmacol Ther 1996; 59, 2: 216) as well as to slightly induce the levels of CYP1A2 (Rost KL et al. Clin Pharmacol Ther 1992; 52: 170–180, Rost KL et al. Clin Pharmacol Ther 1994; 55: 402–411), a CYP isoform distinct from CYP2C19. Some authors have therefore suggested that there might be a need for dosage adjustment in these individuals. The use of the (−)-enantiomer of omeprazole would decrease the potential for CYP1A2 induction in slow metabolisers as a result of the lower plasma levels (AUC) of this compound obtained in these individuals. Since the gastrin levels obtained simply are a result of a natural feedback mechanism determined by the degree of inhibition of gastric acid secretion, the use of the (−)-enantiomer of omeprazole may also potentially result in a less pronounced increase in gastrin in slow metabolisers.

The clinical study reported below supports the claimed invention and discusses the results more in detail.

The (−)-enantiomer of omeprazole is effective as a gastric acid secretion inhibitor, and is useful as an antiulcer agent. In a more general sense, the (−)-enantiomer of omeprazole can be used for prevention and treatment of the same gastric-acid related diseases in mammals and especially in man as omeprazole, see above.

Any suitable route of administration may be employed for providing the patient with an effective dosage of the (−)-enantiomer of omeprazole. For example, oral, parenteral, subcutaneous, intramuscular, rectal, transdermal and the like may be employed. Dosage forms include capsules, tablets, dispersions, suspensions, solutions and the like.

The pharmaceutical compositions of the present invention comprise the (−)-enantiomer of omeprazole as active ingredient, or a pharmaceutically acceptable salt thereof, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. The term "pharmaceutically acceptable salt" refers to both acid and alkaline pharmaceutically acceptable non-toxic salts. Compositions comprising other therapeutic ingredients are especially of interest in the treatment of Helicobacter infections.

The compositions include compositions suitable for oral, rectal or parenteral such as subcutaneous, intramuscular, and intravenous administration. The most preferred route of the present invention is the oral route. The compositions may be conveniently presented in unit dosage forms, and prepared by any methods well known in the art of pharmacy.

The most suitable route of administration as well as the magnitude of a therapeutic dose of the (−)-enantiomer of omeprazole or a pharmaceutically acceptable salt thereof in any given case will depend on the nature and severity of the disease to be treated. The dose, and dose frequency, may also vary according to the age, body weight, and response of the individual patient. Special requirements may be needed for patients having Zollinger-Ellison syndrome, such as a need for higher doses than the average patient. Children and patients with liver diseases generally will benefit from doses that are somewhat lower than the average. Thus, in some conditions it may be necessary to use doses outside the ranges stated below. Such higher and lower doses of the (−)-enantiomer of omeprazole are within the scope of the present invention.

In general, a suitable oral dosage form may cover a dose range from 5 mg to 80 mg total daily dose, administered in one single dose or equally divided doses. A preferred dose range is from 20 mg to 60 mg total daily dose. For a parenteral dosage form the same dose ranges may apply.

The (−)-enantiomer of omeprazole may be combined as the active component in intimate admixture with a pharmaceutical carrier according to conventional techniques, such as the oral formulations described in WO 96/ 01623 and EP 247 983, the disclosures of which are hereby incorporated in a whole by reference.

Different routes of preparation of the (−)-enantiomer of omeprazole and pharmaceutically acceptable salts thereof are described in WO 94/ 27988 and WO 96/ 02535, the disclosures of which are hereby incorporated in a whole by reference.

The invention is further defined by reference to the following experimental work describing in detail the study and results as well as the clinical relevance of the findings.

EXPERIMENTAL STUDY

Methods:

In an open, randomised, three way cross-over designed study, consisting of three treatment periods, each with a duration of 7 days and each separated by a washout period of two weeks, the sodium salt of the (−)-enantiomer of omeprazole, the sodium salt of the (+)-enantiomer of ome-

prazole and omeprazole sodium salt were investigated. Nine healthy subjects, classified according to the urinary S/R mephenytoin ratio as five slow metabolisers and four rapid metabolisers of omeprazole, completed the study (Sanz E. J. et al, Clin Pharmacol Ther 1989; 45:495–499).

In slow metabolisers 60 mg doses of each compound were given once daily, while the rapid metabolisers were given once daily doses of 15 mg. The pharmacokinetics were studied in all subjects on days 1 and 7. The reason for using different doses was to optimise the conditions to explore the secondary aims of the study, to measure the effect on gastric acid secretion in rapid metabolisers and to measure the potential effect on caffeine metabolism in slow metabolisers.

Results and discussion:

In rapid metabolisers the mean AUC at steady state (Day 7) of the (−)-enantiomer of omeprazole was almost 90% higher than that of omeprazole. (FIG. 1). This resulted in a more pronounced gastric acid antisecretory effect for the (−)-enantiomer of omeprazole compared to that of omeprazole. The inhibition of pentagastrin stimulated gastric acid secretion was 62% for omeprazole and 79% for the (−)-enantiomer of omeprazole following administration of 15 mg doses of each substance.

In slow metabolisers the mean AUC at steady state (Day 7) of the (−)-enantiomer of omeprazole was about 30% lower than that of omeprazole. (FIG. 2). Thus, after correction for different dose levels, the resulting difference in AUC between slow and rapid metabolisers was almost 10-fold for omeprazole and only 3-fold for the (−)-enantiomer of omeprazole. With the (+)-enantiomer of omeprazole, on the other hand, the difference in AUC was much greater, approximately 30-fold (FIG. 3).

In conclusion, the interindividual variation in plasma levels upon administration of the (−)-enantiomer of omeprazole will be less than for omeprazole and more patients will get optimal plasma concentrations with respect to gastric acid antisecretory effect and potentially also a better clinical effect following administration of the same doses.

Another study was conducted in 38 patients with symptomatic gastroesophageal reflux disease in which the effects on 24 hour intragastric acidity by oral treatment with 20 mg omeprazole racemate (capsules) and the magnesium salt of (−)-omeprazole (corresponding to 20 mg or 40 mg of the neutral compound) were compared. In addition, the plasma concentrations of (−)-omeprazole and omeprazole racemate were determined on the last treatment day (day 5).

The study was conducted as a double-blind, randomized, three-way cross-over trial consisting of three study periods, each with five days of daily oral administration of formulations containing the magnesium salt of (−)-omeprazole or omeprazole racemate separated by a wash-out period of at least two weeks. The 38 patients (22 females) ranged in age from 29–58 years. 32 of the patients were *Helicobacter pylori* negative.

Enteric coated pellets comprising the magnesium salt of (−)-omeprazole were filled in hard gelatin capsules calculated to correspond to either 20 mg or 40 mg of neutral (−)-omeprazole compound.

These formulations were compared with an identical treatment except for using enteric coated pellets comprising omeprazole filled in a hard gelatin capsule containing 20 mg racemic omeprazole in the non-salt form (Prilosec®).

The intragastric pH was recorded over 24 hours on day five of each study period upon administering the fifth dose.

The study was completed by 36 patients and the results therefrom were statistically evaluated. The effects of the treatments on intragastric pH are summarized in Table 1 and the AUC values are shown in Table 2.

As shown in Table 1 the percentage of time (of the 24-hour period assessed) with pH above 4 (a direct measure of inhibitory effect on gastric acid secretion) was 44% for 20 mg omeprazole racemate and 53% for 20 mg (−)-omeprazole ($p<0.0001$), which means that patients treated with (−)-omeprazole will have 2.2 hours longer time with pH above 4 than those treated with omeprazole racemate in corresponding doses.

TABLE 1

Least square estimates and 95% confidence intervals for the true mean treatment effects, regarding percentage of time with pH > 4 during 24 hours.

Treatment		Estimate	Lower	Upper
Omeprazole	20 mg	43.7	36.7	50.7
(−)ome	20 mg	53.0	46.0	60.0
(−)ome	40 mg	69.8	62.8	76.8

The data of Table 2 shown below demonstrate that the AUC of (−)omeprazole is significantly higher than that of racemic omeprazole at the 20 mg dose, and the 40 mg dose of (−)omeprazole produced a significantly higher AUC than the 20 mg dose of (−)-omeprazole ($p<0.0001$).

The interindividual variation in AUC and thus the inhibitory effect is less pronounced following administration of (−)-omeprazole than following administration of omeprazole racemate. This was judged by the coefficient of variation for the mean AUC which was 59% for 20 mg of the magnesium salt of (−)-omeprazole and 88% for 20 mg of omeprazole racemate ($p<0.0001$).

TABLE 2

Least square estimates and 95% confidence intervals for the true mean treatment effects, regarding AUC (μmol × h/L).

Treatment		Estimate	Lower	Upper
Omeprazole	20 mg	2.3	1.8	3.0
(−)ome	20 mg	4.2	3.3	5.4
(−)ome	40 mg	12.6	9.9	16.2

As a consequence of the less pronounced difference in AUC between slow and rapid metabolizers, the interindividual variation in AUC of (−)-omeprazole is less than that of omeprazole. Furthermore, available data indicate that the interindividual variation in AUC of (−)omeprazole within the group of rapid metabolizers also is less than that observed for omeprazole racemate. These characteristics taken together may potentially result in a larger fraction of patients attaining plasma concentrations which would be optimal with respect to the desired gastric acid anti-secretory effect in the clinical situation.

It was observed that the steady-state AUC of (−)-omeprazole in an average population was significantly higher (2-fold) than that of omeprazole racemate when each compound was given repeatedly in 20 mg daily doses. Therefore, the anti-secretory effect, which is directly correlated to the AUC irrespective of compound, was higher for (−)-omeprazole than for omeprazole racemate following administration of identical doses. This is expected to give a clinical advantage for (−)-omeprazole, since the number of patients healed from the acid-related disease is expected to be higher, and healing is also expected to be achieved within

a shorter time frame. It might also be expected that a more rapid symptom relief will be obtained.

The clinical studies outlined above demonstrate that the alkali metal salts of (–)-omeprazole have unexpected pharmacokinetic advantages over the omeprazole racemate, such as less interindividual variation in plasma levels (AUC) both between rapid and slow metabolizers and within the group of rapid metabolizers. The alkali metal salts of (–)-omeprazole provide for a larger fraction of patients with optimal plasma concentrations with respect to desired antisecretory effect. Higher average AUC results in a more pronounced inhibitory effect on gastric-acid secretion and is expected to result in a better overall clinical effect. Thus, the alkaline salts of (–)-omeprazole can provide an improved, alternative pharmaceutical formulation and method for the treatment of gastric acid-related diseases.

What is claimed is:

1. A method for treatment of gastric acid related diseases by inhibition of gastric acid secretion comprising administering to a mammal in need of treatment a therapeutically effective amount of a proton pump inhibitor consisting essentially of the (–)-enantiomer of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole or a pharmaceutically acceptable salt thereof, so as to effect decreased interindividual variation in plasma levels (AUC) during treatment of gastric acid related diseases.

2. A method for treatment of gastric acid related diseases by inhibition of gastric acid secretion comprising administering to a mammal in need of treatment a therapeutically effective amount of a proton pump inhibitor consisting essentially of the (–)-enantiomer of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole or a pharmaceutically acceptable salt thereof, so as to effect an increased average plasma levels (AUC) per dosage unit.

3. The method according to claim 1 or 2 so as to effect a less pronounced increase in gastrin levels in slow metabolisers during treatment of gastric acid related diseases.

4. The method according to claim 1 or 2 so as to effect a decreased CYP1A induction in slow metabolisers during treatment of gastric acid related diseases.

5. The method according to claim 1 or 2 so as to elicit an improved antisecretory effect during the treatment of gastric acid related diseases.

6. The method according to claim 1 or 2 so as to elicit an improved clinical effect comprising accelerated rate of healing and accelerated rate of symptom relief during the treatment of gastric related diseases.

7. The method according to claim 1 or 2, wherein the (–)-enantiomer of omeprazole or a pharmaceutically acceptable salt thereof, is administered orally in the form of a tablet or a capsule.

8. The method according to claim 1 or 2, wherein the (–)-enantiomer of omeprazole or a pharmaceutically acceptable salt thereof, is administered parenterally.

9. The method according to claim 1 or 2, wherein the (–)-enantiomer of omeprazole or a pharmaceutically acceptable salt thereof, is administered by intravenous infusion.

10. The method according to claim 1 or 2, wherein the amount administered is about 5–80 mg total daily dose.

11. The method according to claim 1 or 2, wherein the amount administered is about 20–60 mg total daily dose.

12. A method for the production of a medicament for treating gastric acid related diseases, which comprises: combining a therapeutically effective amount of a proton pump inhibitor consisting essentially of the (–)-enantiomer of 5-methoxy-2-[[(4-methoxy-3,5dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole or a pharmaceutically acceptable salt thereof, with a pharmaceutically acceptable carrier.

13. The method according to claim 12, wherein the medicament causes a decreased interindividual variation in plasma levels (AUC) per unit dosage during the treatment of gastric acid related diseases.

14. The method according to claim 12, wherein the medicament causes an increased average plasma level (AUC) per unit dosage during the treatment of gastric acid related diseases.

15. The method according to claim 12, wherein the medicament causes a less pronounced increase in gastrin levels in slow metabolisers during treatment of gastric acid related diseases.

16. The method according to claim 12, wherein the medicament causes a decreased CYP1A induction in slow metabolisers during treatment of gastric acid related diseases.

17. The method according to claim 12, wherein the medicament causes an improved antisecretory effect during the treatment of gastric acid related diseases.

18. The method according to claim 12, wherein the medicament causes an improved clinical effect comprising accelerated rate of healing and accelerated rate of symptom relief during the treatment of gastric related diseases.

19. The method according to claim 12, wherein the medicament produced for oral administration is in the form of a tablet or capsule.

20. The method according to claim 12, wherein the medicament is administered parentally, by intravenous infusion.

21. The method according to any of claims 12–20, wherein the medicament is administered in the amount of about 5 mg to 80 mg total daily dose.

22. The method according to any of claims 12–20, wherein the medicament is administered in the amount of about 20 mg to 60 mg total daily dose.

23. The method according to claim 1 or 2 wherein the (–)-enantiomer of the proton pump inhibitor is essentially devoid of its (+)-enantiomeric contaminant.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRRECTION

PATENT NO. : 5,877,192
DATED : March 2, 1999
INVENTOR(S) : Per Lindberg, et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the title page insert the following under item [56]:

U. S. PATENT DOCUMENTS

EXAMINER INITIAL		PATENT NUMBER	ISSUE DATE	PATENTEE	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
		4 6 3 6 4 9 9	1/13/96	Brandstrom et al			
		5 0 4 5 3 2 1	9/3/91	Makino et al			
		4 7 3 8 9 7 4	4/19/88	Brandstrom et al			
		4 8 5 3 2 3 0	8/1/89	Lovgren et al			
		4 7 8 6 5 0 5	11/22/88	Lovgren et al			

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	PUBLICATION DATE	COUNTRY OR PATENT OFFICE	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
		4 0 3 5 4 5 5	11/90	DE				
		0 1 2 4 4 9 5	1/14/87	EP				

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRRECTION

PATENT NO. : 5,877,192
DATED : March 2, 1999
INVENTOR(S) : Per Lindberg, et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER							PUBLICATION DATE	COUNTRY OR PATENT OFFICE	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
		9	6	0	1	6	2	3	1/25/96	WIPO				
		0	0	0	5	1	2	9	4/29/81	EP				
		0	3	6	5	9	4	7	5/2/90	EP				
		9	5	0	1	7	8	3	1/19/95	WIPO				
		9	2	2	2	2	8	4	12/23/92	WIPO				
		9	6	0	2	5	3	5	2/1/96	WIPO				
		9	4	2	7	9	8	8	12/8/94	WIPO				
		6	2	4	7	9	8	3	4/16/87	EP				

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRRECTION

PATENT NO. : 5,877,192
DATED : March 2, 1999
INVENTOR(S) : Per Lindberg, et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

OTHER DOCUMENTS

		Cairns, et al. "Enantioselective HPLC determination..." Journal of Chromatography
		8,666 (1995) 323-328
		Yamada et al. "Synthesis and isomerization of optical active.." Chem. Pharm. Bull.
		42(8) (1994) 1679-1681
		K. Miwa et al. "Jpn. Pharmacol. Ther. "Proton pump inhibitor in rats, mice and dogs"
		18 (1990) 165-187 (transl.)
		H. Katsuki et al. "Determination of R(+)- and S(-)-Lansoprazole" Pharmaceutical
		Research 13(4) (1996) 611-615
		M. Tanaka et al. "Direct determination of pantoprazole enantiomers..." Anal. Chem.
		68 (1996) 1513-1516
		Erlandson et al. "Resolution of the enantiomers of omeprazole..." J. Chromatography
		(1990) 532: 305-319
		Chang et al. 1995 "Interphenotype differences..." Brit. J. Clinical Pharmacology 39: 511-518

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRRECTION

PATENT NO. : 5,877,192
DATED : March 2, 1999
INVENTOR(S) : Per Lindberg, et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

OTHER DOCUMENTS

		A. Brandstrom "Chemical reactions..." Reprint from ACTA CHEMICA SCANDINAVICA"
		43 (1989) 536-611
		K. Sigrist-Nelson et al. "Ro 18-5364, a potent inhibitor of the gastric (H + K) -ATPase"
		Eur. J. Bloch. 166 (1987) 453
		Palomo Coll, Alberto (1992) "Preparation of alkali metal salts of omeprazole..." CA
		No. 117: 90292
		Rost et al. (1994) "Accelerated caffeine metabolism after omeprazole..."
		55: 402-411
		Rost et al. (1992) " Increase of cytochrane P450IA2 activity..."
		52: 170-180
		Marle et al. "Determination of binding affinity of enantiomers..." J. Chromatography
		(1988) 456: 323-336

Signed and Sealed this

Twenty-seventh Day of April, 1999

Attest:

Attesting Officer

Q. TODD DICKINSON

Acting Commissioner of Patents and Trademarks

JS 44 (Rev. 11/04)

CIVIL COVER SHEET

The JS 44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. (SEE INSTRUCTIONS ON THE REVERSE OF THE FORM.)

I. (a) PLAINTIFFS
ASTRAZENECA AB, AKTIEBOLAGET HÄSSLE, ASTRAZENECA LP, KBI INC. and KBI-E INC.

(b) County of Residence of First Listed Plaintiff _____
(EXCEPT IN U.S. PLAINTIFF CASES)

(c) Attorney's (Firm Name, Address, and Telephone Number)
Jack B. Blumenfeld, MORRIS, NICHOLS, ARSHT & TUNNELL LLP, 1201 North Market Street, P.O. Box 1347, Wilmington, DE 19899-1347, (302) 658-9200

DEFENDANTS
TEVA PARENTERAL MEDICINES, INC., TEVA PHARMACEUTICALS USA, INC. and TEVA PHARMACEUTICAL INDUSTRIES LTD.,

County of Residence of First Listed Defendant _____
(IN U.S. PLAINTIFF CASES ONLY)

NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE LAND INVOLVED.

Attorneys (If Known)

II. BASIS OF JURISDICTION (Place an "X" in One Box Only)

- ☐ 1 U.S. Government Plaintiff
- ☒ 3 Federal Question (U.S. Government Not a Party)
- ☐ 2 U.S. Government Defendant
- ☐ 4 Diversity (Indicate Citizenship of Parties in Item III)

III. CITIZENSHIP OF PRINCIPAL PARTIES (Place an "X" in One Box for Plaintiff and One Box for Defendant)
(For Diversity Cases Only)

	PTF	DEF		PTF	DEF
Citizen of This State	☐ 1	☐ 1	Incorporated *or* Principal Place of Business In This State	☐ 4	☐ 4
Citizen of Another State	☐ 2	☐ 2	Incorporated *and* Principal Place of Business In Another State	☐ 5	☐ 5
Citizen or Subject of a Foreign Country	☐ 3	☐ 3	Foreign Nation	☐ 6	☐ 6

IV. NATURE OF SUIT (Place an "X" in One Box Only)

CONTRACT
- ☐ 110 Insurance
- ☐ 120 Marine
- ☐ 130 Miller Act
- ☐ 140 Negotiable Instrument
- ☐ 150 Recovery of Overpayment & Enforcement of Judgment
- ☐ 151 Medicare Act
- ☐ 152 Recovery of Defaulted Student Loans (Excl. Veterans)
- ☐ 153 Recovery of Overpayment of Veteran's Benefits
- ☐ 160 Stockholders' Suits
- ☐ 190 Other Contract
- ☐ 195 Contract Product Liability
- ☐ 196 Franchise

REAL PROPERTY
- ☐ 210 Land Condemnation
- ☐ 220 Foreclosure
- ☐ 230 Rent Lease & Ejectment
- ☐ 240 Torts to Land
- ☐ 245 Tort Product Liability
- ☐ 290 All Other Real Property

TORTS

PERSONAL INJURY
- ☐ 310 Airplane
- ☐ 315 Airplane Product Liability
- ☐ 320 Assault, Libel & Slander
- ☐ 330 Federal Employers' Liability
- ☐ 340 Marine
- ☐ 345 Marine Product Liability
- ☐ 350 Motor Vehicle
- ☐ 355 Motor Vehicle Product Liability
- ☐ 360 Other Personal Injury

PERSONAL INJURY
- ☐ 362 Personal Injury - Med. Malpractice
- ☐ 365 Personal Injury - Product Liability
- ☐ 368 Asbestos Personal Injury Product Liability

PERSONAL PROPERTY
- ☐ 370 Other Fraud
- ☐ 371 Truth in Lending
- ☐ 380 Other Personal Property Damage
- ☐ 385 Property Damage Product Liability

CIVIL RIGHTS
- ☐ 441 Voting
- ☐ 442 Employment
- ☐ 443 Housing/ Accommodations
- ☐ 444 Welfare
- ☐ 445 Amer. w/Disabilities - Employment
- ☐ 446 Amer. w/Disabilities - Other
- ☐ 440 Other Civil Rights

PRISONER PETITIONS
- ☐ 510 Motions to Vacate Sentence

Habeas Corpus:
- ☐ 530 General
- ☐ 535 Death Penalty
- ☐ 540 Mandamus & Other
- ☐ 550 Civil Rights
- ☐ 555 Prison Condition

FORFEITURE/PENALTY
- ☐ 610 Agriculture
- ☐ 620 Other Food & Drug
- ☐ 625 Drug Related Seizure of Property 21 USC 881
- ☐ 630 Liquor Laws
- ☐ 640 R.R. & Truck
- ☐ 650 Airline Regs.
- ☐ 660 Occupational Safety/Health
- ☐ 690 Other

LABOR
- ☐ 710 Fair Labor Standards Act
- ☐ 720 Labor/Mgmt. Relations
- ☐ 730 Labor/Mgmt.Reporting & Disclosure Act
- ☐ 740 Railway Labor Act
- ☐ 790 Other Labor Litigation
- ☐ 791 Empl. Ret. Inc. Security Act

BANKRUPTCY
- ☐ 422 Appeal 28 USC 158
- ☐ 423 Withdrawal 28 USC 157

PROPERTY RIGHTS
- ☐ 820 Copyrights
- ☒ 830 Patent
- ☐ 840 Trademark

SOCIAL SECURITY
- ☐ 861 HIA (1395ff)
- ☐ 862 Black Lung (923)
- ☐ 863 DIWC/DIWW (405(g))
- ☐ 864 SSID Title XVI
- ☐ 865 RSI (405(g))

FEDERAL TAX SUITS
- ☐ 870 Taxes (U.S. Plaintiff or Defendant)
- ☐ 871 IRS—Third Party 26 USC 7609

OTHER STATUTES
- ☐ 400 State Reapportionment
- ☐ 410 Antitrust
- ☐ 430 Banks and Banking
- ☐ 450 Commerce
- ☐ 460 Deportation
- ☐ 470 Racketeer Influenced and Corrupt Organizations
- ☐ 480 Consumer Credit
- ☐ 490 Cable/Sat TV
- ☐ 810 Selective Service
- ☐ 850 Securities/Commodities/ Exchange
- ☐ 875 Customer Challenge 12 USC 3410
- ☐ 890 Other Statutory Actions
- ☐ 891 Agricultural Acts
- ☐ 892 Economic Stabilization Act
- ☐ 893 Environmental Matters
- ☐ 894 Energy Allocation Act
- ☐ 895 Freedom of Information Act
- ☐ 900Appeal of Fee Determination Under Equal Access to Justice
- ☐ 950 Constitutionality of State Statutes

V. ORIGIN (Place an "X" in One Box Only)

☒ 1 Original Proceeding ☐ 2 Removed from State Court ☐ 3 Remanded from Appellate Court ☐ 4 Reinstated or Reopened ☐ 5 Transferred from another district (specify) ☐ 6 Multidistrict Litigation ☐ 7 Appeal to District Judge from Magistrate Judgment

VI. CAUSE OF ACTION
Cite the U.S. Civil Statute under which you are filing (**Do not cite jurisdictional statutes unless diversity**): 35 U.S.C. § 271
Brief description of cause: patent infringement

VII. REQUESTED IN COMPLAINT:
☐ CHECK IF THIS IS A **CLASS ACTION** UNDER F.R.C.P. 23
DEMAND $
CHECK YES only if demanded in complaint:
JURY DEMAND: ☐ Yes ☒ No

VIII. RELATED CASE(S) IF ANY (See instructions): JUDGE See Attachment DOCKET NUMBER _____

DATE April 25, 2008
SIGNATURE OF ATTORNEY OF RECORD Jack Blumenfeld

FOR OFFICE USE ONLY

RECEIPT # _____ AMOUNT _____ APPLYING IFP _____ JUDGE _____ MAG. JUDGE _____

RELATED CASES

1. *AstraZeneca AB; Aktiebolaget Hässle; AstraZeneca LP; KBI Inc.; and KBI-E Inc. v. Ivax Corporation; Ivax Pharmaceuticals NV, Inc.; Ivax Pharmaceuticals, Inc.; Teva Pharmaceuticals Industries, Ltd,; Teva Pharmaceuticals USA; Zenith Laboratories, Inc.*

   C.A. No. 3:06-cv-01057-JAP-TJB (Consolidated into 3:05-cv-05553-JAP-TJB)
   (District of New Jersey)

2. *AstraZeneca AB; Aktiebolaget Hässle; AstraZeneca LP; KBI Inc.; and KBI-E Inc. v. Dr. Reddy's Laboratories, Ltd; Dr. Reddy's Laboratories, Inc.*

   C.A. No. 3:08-cv-00328-JAP-TJB
   (District of New Jersey)

3. *AstraZeneca AB; Aktiebolaget Hässle; AstraZeneca LP; KBI Inc and KBI-E Inc. v. Teva Parenteral Medicines, Inc.; Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries Ltd.*

   Filed April 24, 2008
   (District of New Jersey)

JS 44 Reverse (Rev. 11/04)

INSTRUCTIONS FOR ATTORNEYS COMPLETING CIVIL COVER SHEET FORM JS 44

Authority For Civil Cover Sheet

The JS 44 civil cover sheet and the information contained herein neither replaces nor supplements the filings and service of pleading or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. Consequently, a civil cover sheet is submitted to the Clerk of Court for each civil complaint filed. The attorney filing a case should complete the form as follows:

I. (a) Plaintiffs-Defendants. Enter names (last, first, middle initial) of plaintiff and defendant. If the plaintiff or defendant is a government agency, use only the full name or standard abbreviations. If the plaintiff or defendant is an official within a government agency, identify first the agency and then the official, giving both name and title.

(b) County of Residence. For each civil case filed, except U.S. plaintiff cases, enter the name of the county where the first listed plaintiff resides at the time of filing. In U.S. plaintiff cases, enter the name of the county in which the first listed defendant resides at the time of filing. (NOTE: In land condemnation cases, the county of residence of the "defendant" is the location of the tract of land involved.)

(c) Attorneys. Enter the firm name, address, telephone number, and attorney of record. If there are several attorneys, list them on an attachment, noting in this section "(see attachment)".

II. Jurisdiction. The basis of jurisdiction is set forth under Rule 8(a), F.R.C.P., which requires that jurisdictions be shown in pleadings. Place an "X" in one of the boxes. If there is more than one basis of jurisdiction, precedence is given in the order shown below.

United States plaintiff. (1) Jurisdiction based on 28 U.S.C. 1345 and 1348. Suits by agencies and officers of the United States are included here.

United States defendant. (2) When the plaintiff is suing the United States, its officers or agencies, place an "X" in this box.

Federal question. (3) This refers to suits under 28 U.S.C. 1331, where jurisdiction arises under the Constitution of the United States, an amendment to the Constitution, an act of Congress or a treaty of the United States. In cases where the U.S. is a party, the U.S. plaintiff or defendant code takes precedence, and box 1 or 2 should be marked.

Diversity of citizenship. (4) This refers to suits under 28 U.S.C. 1332, where parties are citizens of different states. When Box 4 is checked, the citizenship of the different parties must be checked. (See Section III below; federal question actions take precedence over diversity cases.)

III. Residence (citizenship) of Principal Parties. This section of the JS 44 is to be completed if diversity of citizenship was indicated above. Mark this section for each principal party.

IV. Nature of Suit. Place an "X" in the appropriate box. If the nature of suit cannot be determined, be sure the cause of action, in Section VI below, is sufficient to enable the deputy clerk or the statistical clerks in the Administrative Office to determine the nature of suit. If the cause fits more than one nature of suit, select the most definitive.

V. Origin. Place an "X" in one of the seven boxes.

Original Proceedings. (1) Cases which originate in the United States district courts.

Removed from State Court. (2) Proceedings initiated in state courts may be removed to the district courts under Title 28 U.S.C., Section 1441. When the petition for removal is granted, check this box.

Remanded from Appellate Court. (3) Check this box for cases remanded to the district court for further action. Use the date of remand as the filing date.

Reinstated or Reopened. (4) Check this box for cases reinstated or reopened in the district court. Use the reopening date as the filing date.

Transferred from Another District. (5) For cases transferred under Title 28 U.S.C. Section 1404(a). Do not use this for within district transfers or multidistrict litigation transfers.

Multidistrict Litigation. (6) Check this box when a multidistrict case is transferred into the district under authority of Title 28 U.S.C. Section 1407. When this box is checked, do not check (5) above.

Appeal to District Judge from Magistrate Judgment. (7) Check this box for an appeal from a magistrate judge's decision.

VI. Cause of Action. Report the civil statute directly related to the cause of action and give a brief description of the cause. **Do not cite jurisdictional statutes unless diversity.** Example: U.S. Civil Statute: 47 USC 553
Brief Description: Unauthorized reception of cable service

VII. Requested in Complaint. Class Action. Place an "X" in this box if you are filing a class action under Rule 23, F.R.Cv.P.

Demand. In this space enter the dollar amount (in thousands of dollars) being demanded or indicate other demand such as a preliminary injunction.

Jury Demand. Check the appropriate box to indicate whether or not a jury is being demanded.

VIII. Related Cases. This section of the JS 44 is used to reference related pending cases if any. If there are related pending cases, insert the docket numbers and the corresponding judge names for such cases.

Date and Attorney Signature. Date and sign the civil cover sheet.